cal heterogeneity are reduced. Such families will have sufficient power to accept or reject linkage by themselves and to allow formal tests of heterogeneity. The informative families analyzed by Hecht et al. (1991*a*) were not sufficiently large to fulfill these conditions.

The "multiplex monogenic" strategy is splendid when it generates a true positive result (e.g., Alzheimer disease and chromosome 21); however, we anticipate that apparent exclusions will be frequently overinterpreted. This will lead to erroneous exclusion of important susceptibility loci for complex traits after linkage analysis using overly simple genetic models.

In conclusion, the nature of the association between TGFA polymorphisms and CL/P should be explored in a linkage study under an appropriate genetic model. The genotypic association data show that TGFA is a susceptibility locus of modest effect, and this should be allowed for in the specification of genetic models for linkage analysis. Analysis under an inappropriate model may result in erroneous exclusion of a candidate susceptibility locus. Although it is impossible to know the minimum number of families to collect to ensure a good chance of detecting linkage, the maximum number of families *can* be calculated. If studies are designed in this way, then the paradox of inability to confirm linkage in the face of overwhelming evidence of association can be avoided.

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Reply to Farrall et al.

To the Editor:

Farrall et al. point out the dilemma that investigators working on cleft lip with or without cleft palate (CL(P)) have been facing; that is, the heritability of clefting does not fit a straightforward pattern of inheritance. Complex segregation analyses have yielded varying results with major-gene locus, mixed, and multifactorial/

threshold models being implicated by one or more studies (Chung et al. 1986; Marazita et al. 1986, 1992; Hecht et al. 1991*b*). The association of transforming growth factor alpha (TGFA) and CL(P) is fascinating and important and may provide some important insights into the etiology of clefting. There are now three studies (Ardinger et al. 1989; Chenevix-Trench et al. 1991; Holder et al. 1992) confirming and one study (Qian et al. 1991) not confirming the association. However, while we agree that sample-size considerations are important in linkage studies, the results of both our linkage study and an independent linkage study from England have shown that TGFA is not linked to CL(P) in the tested multiplex families (Hecht et al. 1991*a*; Holder et al. 1992). It is also interesting that the same investigators (Vintiner et al. 1992) found an association between TGFA in a group of individuals with CL(P) but found no evidence of linkage when multiplex families were studied (Holder et al. 1992). In fact, their linkage results were strikingly similar to our study results. These linkage studies *do* exclude TGFA as a major gene in these tested families. Further, there is a possibility that TGFA may play an epistatic role in the development of clefting but that it is not the major gene (J. C. Murray, personal communication). This is the same conclusion that we found in our linkage study. Further, we specifically concluded that TGFA may be linked in other multiplex CL(P) families. Additional families are now being tested.

Among the 20 combined multiplex CL(P) families from both published studies (Hecht et al. 1991*a*; Holder et al. 1992), the C2 allele was identified in 4 families and did not segregate with the putative disease locus. It will be interesting to study additional multiplex CL(P) families with the C2 allele, to determine whether it is linked in those families. For now, the association- and linkage-study results suggest that the causes of CL(P) are heterogeneous. Time and future studies will explain the probable myriad of causes that contribute to and cause facial clefting.

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Forensic Population Genetics and the National Research Council (NRC)

To the Editor:

In response to calls from the scientific and legal communities, the Board on Biology of the National Research Council established a Committee on DNA Technology in Forensic Science. This committee has now issued a